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Novel Therapies for Intracerebral Hemorrhage

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INTRODUCTION

Intracerebral hemorrhage is by far the most destructive form of stroke[1]. Apart from the management in a specialized stroke or neurological intensive care unit (NICU), no specific therapies have been shown to consistently improve outcomes after ICH[2]. Current Guidelines endorse early aggressive optimization of physiologic derangements with ventilatory support when indicated, blood pressure control, reversal of any preexisting coagulopathy, intracranial pressure monitoring for certain cases, osmotherapy, temperature modulation, seizure prophylaxis, treatment of hyerglycemia, and nutritional support in the stroke unit or NICU. Ventriculostomy is the cornerstone of therapy for control of intracranial pressure patients with intraventricular hemorrhage.[3,4] Surgical hematoma evacuation does not improve outcome for most patients, but is a reasonable option for patients with early worsening due to mass effect due to large cerebellar or lobar hemorrhages. Promising experimental treatments involve targeting of molecular mechanisms implicated in inflammation, blood product degradation, and secondary neuronal damage.

NOVEL THERAPIES FOR ICH

Ultra-early hemostatic therapy

Hematoma volume is an important determinant of mortality after ICH and early hematoma growth which is the increase in hematoma size within 6 hrs of onset, is consistently associated with poor clinical outcomes and an increased mortality.[5-8] Recombinant factor VII (rFVIIa, Novoseven®, Novo Nordisk), a powerful initiator of hemostasis, was studied in a randomized, double blind, placebo-controlled study, in which 399 patients with spontaneous ICH received treatment with rFVIIa at doses of 40, 80, or 160 µg/kg within four hours after ICH onset. Use of rFVII was associated with a 38% reduction in mortality and significantly improved functional outcomes at 90 days despite a five percent increase in the frequency of arterial thromboembolic adverse events.[9] The phase III FAST study compared doses of 80 and 20 µg/kg of rFVIIa with placebo in an overall trial population of 841 patients. No significant difference was found in the main outcome measure, which was the proportion of patients with death or severe disability according to the modified Rankin scale at 90 days (score of 5 or 6 but the hemostatic effect and side effect profiles were confirmed.[10] On the basis of these results, routine use of rFVIIa as a hemostatic therapy for all patients with ICH within a four-hour time window cannot be recommended. The lack of effect of rfVII in ICH, despite its ability to halt hematoma expansion, suggests that additional or targeted therapy to sub-groups of patients may alter the outcome after ICH. In a FAST trial sub-group analysis, a potential effect of rFVII was seen in patients <70 years, baseline hematoma volumes of <60ml, baseline IVH <5ml and time from onset <2.5hrs[11]. Future research is needed to address to potential effects of rFVII in this sub-groups and if the use of CT technology can improve the identification of candidates for rFVII.[12]

Argatroban

A potent inhibitor of fibrin-bound and free thrombin has been used successfully as an alternative for anticoagulation in patients with heparin-induced thrombocytopenia, acute ischemic stroke, and vascular occlusive disease. Animal models have shown that this agent reduces brain edema within six hours of administration and therefore, may be an effective therapy for hematoma-induced edema.

Minocycline

A type of tetracycline has been associated with neuroprotective properties related to MMP inhibition, antioxidant and anti-inflammatory activity. The effects of this agent have demonstrated in experimental models of ICH.[13-15]

Deferoxamine

A potent iron-chelating compound promotes excretion of iron when administered orally or intravenously. Based on the toxicity of iron and oxidative stress related to hematoma, deferoxamine was shown to reduce ICH mediated peri-lesional brain injury in rats[16] and piglets[17] injected with autologous blood into the basal ganglia.

Statins

Rosuvastatin, a potent statin used for reduction of cardiovascular risk was used in a small study of ICH patients providing modest benefits.[18]

Free radical scavenger (NXY-59)

In a recent clinical trial, the effects of NXY-59, a free radical scavenger, were investigated in 607 patients with ICH. NXY-59 was associated with slightly less hematoma growth than placebo at 72 hrs after treatment but without effect on mortality or functional outcomes at 3 months.[19]

Pioglitazone

A thiazolidinedione is currently approved for the management of type II diabetes mellitus and found to modulate peroxisome proliferator-activated receptor gamma agonists in microglia and macrophages, has demonstrated the ability to increase hematoma reabsorption and neuronal protection in animal models.[20] A phase II clinical trial is currently underway to test the hypothesis that pioglitazone is safe and tolerable after ICH.[21] Additional human trials with deferoxamine,[22] statins[23] are currently underway.

Temperature modulation (TTM)

Temperature control could potentially offer benefits related to metabolic control, ICP control, and inhibition of the inflammatory cascade, which is associated with apoptosis and neuronal death[24,25]. Hyperthermia is considered to have detrimental effects to the injured brain and may well be an initial response to the initial ictus [26] Several studies have shown the direct association between hyperthermia and poor outcomes after all types of brain injury.[26-28] Szczudlik et al[29] showed that ICH patients with onset of hyperthermia on the first day of hospitalization have greater mortality and worse functional status 30-days after the ictus. Sustained fever has been shown to be independently associated with poor outcome after ICH.[29] A large body of experimental evidence indicates that even small degrees of hyperthermia can worsen ischemic brain injury by exacerbating excitotoxic neurotransmitter release, proteolysis, free radical and cytokine production, blood-brain barrier compromise, and apoptosis[30], [31]. Brain temperature elevations have also been associated with hyperemia, exacerbation of cerebral edema, and elevated intracranial pressure.[32,33] Recent experimental data from animal models of ICH that used bacterial collagenase infusions, suggested that temperature modulation improved recovery and lessened neuronal injury when hypothermia was initiated after 12-hours of onset[34] but this effect was not seen in a different animal model of "whole blood" infusion.[35] A recent study of ICH patients suggested that mild induced hypothermia was associated with less cerebral edema without change in hematoma growth or functional outcome when hypothermia was started after 6-hours of onset.[36] The American Heart Association (AHA) has recommended normothermia in the setting of acute ICH.[37] No method to accomplish this has been evaluated in a prospective fashion. Although acetaminophen and cooling blankets are generally used, efficacy in the intensive care setting has been questioned.[38]

Craniotomy and clot evacuation

Craniotomy has been the most studied intervention for the surgical management of ICH. Two earlier smaller trials showed that for patients presenting with moderate alterations in the state of consciousness, surgery reduced the risk of death without improving the functional outcome[39] and that ultra-early evacuation of hematoma improved the 3-month NIHSS[40] without an effect in mortality but a meta-analysis of all prior trials of surgical intervention for supratentorial ICH showed no significant benefit from this intervention.[41] The STICH study, a landmark trial of over 1000 ICH patients, showed that emergent surgical hematoma evacuation by craniotomy within 72 hours of onset fails to improve outcome compared to a policy of initial medical management.[42] In a post-hoc analysis of STICH, the sub-group of patients with superficial hematomas and no IVH had better outcomes in the surgical arm.[43] This observation provided support for the STICH-II trial, which is currently enrolling patients. In contrast to supratentorial ICH, there is much better evidence that cerebellar hemorrhages exceeding 3 cm in diameter benefit from emergent surgical evacuation as abrupt and dramatic deterioration to coma can occur within the first 24 hours of onset in these patients.[44] For this reason, it is generally unwise to defer surgery in these patients until further clinical deterioration occurs.

Emergency hemicraniectomy

Hemicraniectomy with duraplasty has been proposed as a life-saving intervention for several neurological catastrophes such as malignant MCA infarction and poor grade SAH. No randomized controlled trial has been conducted in patients with ICH. In a recent report of 12 consecutive patients with hypertensive ICH and treated with hemicraniectomy, 92% survived at discharge and 55% had a good functional outcome at discharge.[45] This preliminary data supports the need for better-controlled studies addressing the role of this surgical technique in ICH patients.

Minimally invasive surgery (MIS)

The advantages of MIS over conventional craniotomy include reduced operative time, the possibility of performance under local anesthesia, and reduced surgical trauma. Endoscopic aspiration of supratentorial ICH was studied in a small single-center randomized controlled trial.[46] The study showed that this technique provided a reduction of mortality at 6 months in the surgical group but surgery was more effective in superficial hematomas and in younger patients (<60 years).[46] Similarly, a recent report from China evaluated the effects of minimally invasive craniopuncture versus medical therapy in a cohort of 465 patients with basal ganglia ICH. Improvement in neurological outcome at 14 days and 3-months was better in the treatment group, though no differences were seen in long-term mortality.[47]

Thrombolysis and clot evacuation

Thrombolytic therapy and surgical removal of hematomas is another technique that has been studied in a single center randomized clinical trial.[40] Patients in the surgical group had better outcome scores than the medically treated group. Finally, a multi-center randomized control trial examined the utility of sterotactic urokinase infusion when administered within 72hrs to patients with GCS $\geq$ 5 and hematomas $\geq$10ml provided significant reduction in hematoma size and mortality rate at expense of higher rates of rebleeding but no significant differences in outcomes measures was seen.[48]

Thrombolysis after IVH

Intraventricular administration of the plasminogen activator urokinase every 12 hours may reduce hematoma size and the expected mortality rate at one month.[49] Several small studies have

reported the successful use of urokinase or tissue plasminogen activator (t-PA) for the treatment of IVH, with the goal of accelerating the clearance of IVH and improving clinical outcome.[50] A Cochrane systemic review published in 2002 summarized the experience of several case series providing evidence of safety but no definitive efficacy.[51] The ongoing Phase III Clear IVH Trial (Clot Lysis Evaluating Accelerated Resoution of Intra Ventricular Hemorrhage) is designed to investigate the optimum dose and frequency of r-tPA administered via an EVD to safely and effectively treat IVH and will soon provide some insight on this issue. When used off-label, a dose of 1 mg of rt-PA every eight hours (followed by clamping of the EVD for one hour) is reasonable until clearance of blood from the third ventricle has been achieved. Doses of 3 mg or more of t-PA for IVH thrombolysis have been associated with an unacceptably high bleeding rate.

CONCLUSION

Recent attempts to discern the pathophysiology of ICH have provided meaningful information to support plausible targets for intervention but evidence based therapies for ICH are not yet available. Treatment is primarily supportive and outcomes remain poor. Despite a long history of devastating outcomes and high mortality, there is still optimism that the management of ICH will change in the future based on new insights into the acute pathophysiology of this disease. A better understanding of the dynamic process of hematoma growth, importance of inflammation triggered by coagulation and products of blood degradation, and the deleterious effects of fever and inflammation may provide feasible targets for future interventions. Additional invasive and non-invasive treatment strategies are being tested in clinical trials and results are forthcoming.

Conflicts of Interest

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Dr. Rincon is consultant advisor for: Otsuka and Bard Medical

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